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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 20040428

Application Number: 09/900,063
Filing Date: July 06, 2001
Appellant(s): ROTHSCHILD ET AL.

Heidi Nebel
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed March 17, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that the claims do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Thisted et al notes (http://www.stat.uchicago.edu/~thisted)

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-3, 7-11, 14, 16-20, 26-29, 36-38, 40, 41, 45, 49, 54 and 55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a genus of nucleic acids which comprise prolactin receptor polymorphisms which are not disclosed in the specification. The genus includes an enormous number of polymorphisms for which no written description

is provided in the specification. This large genus is represented in the specification by only the particularly named four polymorphisms for which data is provided demonstrating an association with the phenotypic trait, litter size. Thus, applicant has express possession of only four particular polymorphisms, in a genus which comprises hundreds of millions of different possibilities. Here, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. Even in the narrower dependent claims, such as claim 7, where MseI is required, no specific polymorphism is named. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with litter size is provided. Further, these claims expressly encompass all the different possible allelic variants including insertions, deletion, substitutions and transversions at thousands of different sites. No written description of alleles, of upstream or downstream regions containing additional sequence, which are associated with any phenotype are described in the specification.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one

> might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition in claim 1 of a polymorphism associated with litter size which lacks any specific structure, is precisely the situation of naming a type of material which is generally known to likely exist, but, except for the four specific polymorphisms, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim to "a polymorphism in the prolactin receptor gene", for example.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely but its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which comprise prolactin receptor polymorphisms. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

3. Claims 1-3, 7-11, 14, 16-20, 26-29, 36-38, 40, 41, 45, 49, 54 and 55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some polymorphisms in the porcine prolactin receptor such as the Alu polymorphism, does not reasonably provide enablement for all polymorphisms including the MseI polymorphism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of screening animals for polymorphisms in the prolactin receptor gene which are associated with increased litter size. The invention is is the class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are broadly drawn to encompass a method of screening for any polymorphism in the prolactin receptor gene. In fact, claim 40 as amended is now open to screening for any polymorpism in any gene whatsoever, in any species. Even the narrow claim 7 is drawn to any polymorphism which can be detected by the use of the MseI restriction enzyme. The method broadly encompasses the use of the method in any type of mammalian patient. This means that the method is broadly drawn to the use, not only of pigs, but also of sheep, bats, whales or any other mammal. Further, the animals undergoing the screening may contain any of a number of complicating variables, since the background genotype with regard to other genes may play significant roles in the effect on litter sizes.

Quantity of Experimentation

The quantity of experimentation in this area is very large since there is significant variability in the effects of polymorphisms on phenotypes such as litter size. Screening each possible polymorphism in the prolactin receptor gene represents an inventive, unpredictable and difficult undertaking in itself. As shown in the results on page 46, over 1500 litters were analyzed involving literally hundreds of pigs. This would require

years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The specification demonstrates the unpredictability of this invention, since the P values identified by the specification for the association of the MseI SNP with litter size are 0.2 and 0.3. As Thisted et al notes (See http://www.stat.uchicago.edu/~thisted) "It has become scientific convention to say that p-values exceeding 0.05 (one in twenty) just aren't strong enough to be the sole evidence that two treatments being studied really differ in their effect (see page 5)". Thus, by scientific convention, the data presented for the Mse1 SNP on page 46 of the specification fails to demonstrate a statistically significant effect. It is highly unpredictable whether the SNP is, in fact, associated with the increased litter size. Unlike the Alu1 polymorphism, shown on page 36, where there is a P value below 0.05, the Mse1 polymorphism fails to show a significant effect. The factor of unpredictability weighs against the enablement of the claims.

Working Examples

The specification has a working example where an Alu polymorphism is clearly associated with litter size.

Guidance in the Specification.

The specification, while suggesting an association between the MseI SNP and litter size, did not provide sufficience evidence to demonstrate the association.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching that the P values are insufficient are opposed to enablement of the invention (see Thisted above). The specification provides one with no written description or guidance that leads one to a reliable method where an MseI polymorphism is associated with litter size. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Further the specification does not provide guidance to overcome art and specification recognized problems in the use of polymorphisms as prognostic of litter size as broadly claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the specific polymorphism at issue and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

(11) Response to Argument

Written Description

The first issue is whether the claims comply with the written description requirement of 35 U.S.C. 112, first paragraph. In this analysis, Appellant correctly sets

forth the legal framework which underlies the written description analysis. Appellant correctly notes that a structure function relationship is required by the Federal Circuit in Lilly to support a generic claim under the written description requirement. Appellant also correctly notes that a "representative number of species" is required and cites the USPTO written description guidelines which notes that in an unpredictable art, a single species is not sufficient to describe the genus.

It is not, however, the presence of specific polymorphisms within SEQ ID NO: 3 which fail the association test that supports the written description rejection. It is the absence of any structure function relationship and the absence of a representative number of species which supports the conclusion that there is insufficient descriptive support for the current claims. This argument rests on three grounds. First, the polymorphisms shown are not representative of the genus of any polymorphism associated with litter size. Second, the claims are defined entirely by function and there is no structure function relationship between undisclosed polymorphisms in the prolactin receptor sequence and litter size. Third, nearly all of the claims are drawn to screening for polymorphisms in any animal, using the prolactin receptor gene sequence of a pig, so that there is no structure or function present for any animal other than pig.

Absence of a representative number of species

In the current case, the first question is what constitutes a generic claim. The genus of polymorphisms represents every possible variation which could occur in SEQ ID NO: 3, including multiple polymorphisms within the sequence. In order to provide a representative number of species, in a genus which contains literally hundreds of

billions of different members, the court in Lilly required "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. (Lilly at page 1406)." Lilly continues to note that in other cases, two chemical compounds in a subgenus were insufficient to describe that genus. In the current case, Appellant argues that three polymorphisms are shown to be linked with litter size, AluI, HinFI, and Hpych21V. This is not consistent with the specification, which states at page 45, that "There was no sow line x SNP interaction for HinFI (P>0.5)." At the same page, the specification shows that the MseI polymorphism also lacks a statistical association with litter size, with a P value of 0.2. So at best, Appellant has shown two species in the genus of all possible polymorphisms, the AluI and Hpych21V polymorhisms, which are associated with litter size. These two species represent single nucleotide polymorphic changes and are not representative in any way of each other, or of the genus.

Absence of any structure-function relationship

The second issue is whether there is any structure function relationship which correlates the function, increased litter size, with a particular structure. This question fundamentally addresses the issue of whether there is any structure which the specification demonstrates is necessarily correlated with the function of increased litter size. In this case, the answer is no, there is no structure given, other than the two specific polymorphisms, which is associated with increased litter size.

Conceptually, at minimum a polymorphism is a single nucleotide change in a DNA sequence. It may represent a larger change, including a deletion, an insertion or multiple changes, but minimally consists of a single nucleotide change. To describe such a change, both possible nucleotides at the position of interest must be disclosed. It is insufficient to describe a polymorphism as, hypothetically, an Adenine at position 57, because this is not a polymorphism, just a sequence. In order to be a polymorphism, the description must state, for example, a Guanosine for Adenine change at position 57. So the description of a sequence is not a description of a polymorphism, since the sequence alone does not provide the structure of the change that IS the polymorphism.

So instant claim 1, for example, provides no description of any polymorphism whatsoever. Further, the specification provides a description of only four polymorphisms, only two of which, AluI and Hpych21V, are associated with litter size. There is no structure in commone between the specific nucleotide change at the AluI polymorphism and the Hpych21V polymorphism. More importantly, there is no structure in common between the specific change at either of the disclosed polymorphisms and any other polymorphism which may exist. This is because there is nothing in common between having a G to A change at position 57 and having a C to A change at position 93 or a G to T change at position 105 or even having a G to A change at position 33 (all of which are hypothetical changes). Even the G to A change at position 33 shares no structural relationship with the G to A change at position 57 because each of these

changes occurs in distinct sequence regions, with distinct effects and with no necessary relationship. So there is no common structure between polymorphisms.

The presence and existence of the two polymorphisms in the prolactin receptor sequence shown by Appellant does not even necessarily demonstrate that the prolactin receptor itself is necessarily involved in litter size and consequently, the structure of SEQ ID NO: 3 is not necessarily even relevant. These polymorphisms may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in litter size may be tens of thousands of nucleotides distant from the polymorphisms in the prolactin receptor gene.

When Appellant argues that not every polymorphism may be associated with an increase in litter size, but the method may be used to locate such polymorphisms, Appellant's argument supports the conclusion of the rejection. If there were a structure/function relationship, then there would be a capacity to determine which species would function based upon some shared structural element. But since there is no common structure among the polymorphisms that is associated with the function of litter size, there is no structure-function relationship between the genus of polymorphisms claimed and the function of increased litter size in the claims.

The claim scope broadly encompasses all animals

The species are particularly non-representative when it is realized that the two species for which any association is shown (as well as the two species which lack association) are found in pig. Most of the claims (excluding claims 8, 36-38 and 55) are not limited to pigs. These claims are open to any animal in the world, whether a

mammal or not. While prolactin is likely found only in mammals (which lactate), the size of the genus is increased exponentially when the claim is open to all possible mammals. The genus is immense in pigs alone, and is even larger when zebras, whales, mice, horses or marmosets are included. For this vast genus, only two species are provided. Thus, the conclusion is inescapable that the specification fails to provide a representative number of species in the immense genus of polymorphisms possible in the pig prolactin sequence and even larger genus of all animals with a prolactin receptor.

Further, the structure function relationship is also more attenuated, since the sequence provided is the pig prolactin receptor gene, but the claim is drawn to the any polymorphism in any prolactin receptor gene or "region thereof" from any species. This is the precise case found in Lilly, where disclosure of a DNA sequence of one species did not provide descriptive support for generic claims to any species. The current claim fails to provide structure for a "region" or the prolactin receptor gene of any animal. Therefore, the claim fails to comply with the written description requirement of 35 U.S.C. 112, first paragraph.

Enablement

Appellant does not specifically address each of the Wands factors but rather argues selection of variants is routine. This is not correct because it is entirely unpredictable if there are variants. In fact, Appellant is attempting to claim this subject matter because it is not routine. It is entirely unpredictable and inventive whether any particular polymorphism is associated with litter size. In particular, this unpredictability,

combined with the other factors, supports a conclusion of undue experimentation. Unlike the simple screening assay in Wands itself, where experimental success was assured so long as sufficient resources were expended, since eventually an antibody producing cell would be isolated, here there is no assurance or even likelihood of success, since there is no reason to believe that other polymorphisms necessarily exist which have the desired correlation. At the time of the invention, it is speculative and without evidentiary basis to predict if there will be any results from the screening for additional polymorphisms, unlike Wands where it is not only possible but expected that results will be achieved. Here, there is no expectation that other polymorphisms associated with litter size will be found.

When Appellant argues that another inventor, who found a polymorphism in the prolactin receptor sequence that was not disclosed by Appellant, should be deemed an infringer, Appellant is supporting the rejection. Appellant wishes to claim coverage of polymorphisms which Appellant did not find, did not disclose as associated with litter size and of which Appellant was entirely unaware.

Appellant states "Polymorphisms exist within the prolactin receptor gene which allow one skilled in the art to select those animals which are likely to produce larger litters." This statement is not entirely correct. Two polymorphisms that show such an association exist in the pig prolactin receptor gene. There is no evidence of any such polymorphisms in any other animal. There is no evidence of any other polymorphisms in the pig prolactin receptor gene which share this correlation. Since Appellant screened several breeds of pigs, it may be that the polymorphism is not a marker of

litter size persay, but rather a marker for a breed of pigs which has increased litter size and there is, in fact, no direct association with litter size at all.

Appellant then argues that three polymorphisms are shown to be linked with litter size, AluI, HinFI, and Hpych21V. This is not consistent with the specification, which states at page 45, that "There was no sow line x SNP interaction for HinFI (P>0.5)." At the same page, the specification shows that the MseI polymorphism also lacks a statistical association with litter size, with a P value of 0.2. So at best, Appellant has shown two species in the genus of all possible polymorphisms, the AluI and Hpych21V polymorhisms, which are associated with litter size.

The first issue that not specifically addressed by Appellant is the scope of the claim. The claim is open to any species. Appellant has provided no evidence that the prolactin receptor gene is associated with litter size in any other species of animal besides pig and has provided no polymorphisms in any animal besides pig. So even if pig was deemed enabled, which it is not, the claim is overbroad since it encompasses every animal species, from whales to wombats. The further broad scope is indicated by the "regions thereof" language relating to SEQ ID NO: 3, indicating that the claim is not limited to the full length sequence but is open to shorter, undisclosed fragments of SEQ ID NO: 3.

The second issue that is not specifically addressed is the unpredictability of the invention as it relates to the quantity of experimentation. In order to identify polymorphisms associated with litter size, hundreds of animals need to be screened to identify polymorphisms, with multiple variant litters, in multiple different regions of the

prolactin receptor gene. While pigs (and perhaps mice) breed in large numbers with large litters, many animals within the scope of these claims, such as cows, sheep and horses, (to select more ordinary animals), do not breed in large numbers and typically have small litters, including only one birth at a time. It would require immense amounts of experimentation and an entirely undue quantity of experimentation to determine polymorphisms associated with litter size in these animals, since it would require many thousands of animals to be screened and there is no predictability that there is a single polymorphism associated with litter size in these animals.

The unpredictability is the central concern. Even in Appellant's own study, two polymorphisms failed to provide significant results. Appellant even now argues that there are three polymorphisms which show association, but the specification found a P value >0.5 for HinF1, demonstrating that it is entirely unpredictable which, if any, polymorphisms are associated with litter size.

The conclusion of undue experimentation is based upon an analysis of all of the Wands factors. When all of these factors are considered, the broad scope of the claim, the unpredictability of the claim, the immense amount of experimentation required, the very limited showing of two polymorphisms in pigs, the lack of description of other polymorphisms or polymorphisms in other animals in the specification, the unpredictable nature of the invention, balanced only against skill in the art, the conclusion is clear that undue experimentation is required.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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4/21/04

April 29, 2004

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